American Chemistry Council | SEHSC Silicones Environmental, Health, and Safety Center

Via CDX Electronic Submission

March 4, 2019

TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428
Attn: Section 8(e)
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20004-3302

RE: Supplemental Submission to May 30, 2018 TSCA 8(e) Submission: Triethoxyphenylsilane (CAS No. 780-69-8) (8EHQ-18-21309)

Dear TSCA 8(e) Coordinator:

In accordance with the provisions of 8(e) of the Toxic Substances Control Act (TSCA), the Silicones Environmental, Health, and Safety Center (SEHSC) of the American Chemistry Council hereby submits this supplemental letter to our initial TSCA Section 8(e) notification of May 30, 2018 (8EHQ-18-21309) on behalf of its member companies[1]. This letter is to inform EPA of additional findings from the study titled "Combined Repeated Dose Oral Toxicity Study with the Reproduction / Developmental Toxicity Screening Test in Wistar Rats with Triethoxyphenylsilane (CAS 780-69-8) including a 14-Day Recovery Period". The study report has not been finalized yet, as a scientific discussion on the findings is still ongoing. At this time, neither SEHSC nor any of its member companies has made a determination as to whether a significant risk or injury to human health or the environment is actually presented by the findings.

Summary

The aim of this study was to assess the possible effects of Triethoxyphenylsilane (CAS 780-69-8) on male and female fertility and embryofetal development after repeated dose administration in Wistar rats following OECD TG 422.

The data below demonstrates that the NOAEL of Triethoxyphenylsilane in this study for general toxicity may be considered to be 40 mg/kg bw/day and for reproductive toxicity screening is considered to be 360 mg/kg bw/day.

The following doses were evaluated:

Control:	0 mg/kg body weight
Low Dose:	40 mg/kg body weight
Medium Dose:	120 mg/kg body weight
High Dose:	360 mg/kg body weight

[1] SEHSC is a not-for-profit trade sector group whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Center is comprised of North American silicone chemical producers and importers.

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The test item formulation was used within 10 days after preparation. The test item was emulsified in corn oil and administered daily during 14 days of pre-mating and 14 days of mating in both male and female animals, during the gestation period and up to post-natal day 12 in females. Males were dosed for 28 days. Dose volumes were adjusted individually based on weekly body weight measurements. The administration volume was 4 mL/kg body weight.

Summary of Results

Mortality:
One male animal from the HD group (no. 92) had to be euthanised due to a moribund condition on study day 15, showing the following clinical symptoms: markedly reduced spontaneous activity, prone position, slight salivation, wasp waist, dehydration, moderate piloerection, hypothermia, abnormal breathing. Both kidneys of this animal were enlarged and one kidney was white and of viscous consistency. Ureters were dilated.

Histopathologically, the cause of the mortality is assumed to be a consequence of backflow nephrosis. It is considered to be a treatment related finding. All other rats survived until the end of the study period.

Clinical Observations:
There were clinical signs related to systemic toxicity during the treatment and recovery periods. The clinical signs such as salivation and moving the bedding were observed immediately after the dose administration was considered to be a sign of discomfort due to a local reaction to the test item rather than a systemic adverse effect and has no toxicological relevance. There were no adverse clinical signs. None of the females showed signs of abortion or premature delivery. During the weekly detailed clinical observations, no relevant differences between the groups were found.

Body Weight Development:
Triethoxyphenylsilane (CAS 780-69-8) had an effect on body weight in the HD group of this study.
Body weights of the HD group males were approximately 10 % below controls (at the end of treatment) and those of females up to approximately 11 % below controls (at the end of gestation and start of the lactation period).

During the recovery period there were no changes of toxicological relevance in body weight of HD animals, when compared to controls.

The significant but reversible effect on mean body weight and body weight gain in HD group male and females was considered as test item related and toxicologically relevant.

Body weight development of MD and LD animals was not considerably different from controls.

Food Consumption:
In males of the HD group food consumption was slightly lower during the premating period when compared to controls. In females of this group the same effect was observed during the gestation period (GD 7 to 20). No effect of Triethoxyphenylsilane (CAS 780-69-8) on food consumption of the MD and LD animals was observed.

The effect on food consumption in HD and HD recovery males and females during the treatment period was considered to be test item related and toxicologically relevant.

Food consumption of males and females during the recovery period was comparable between HD group and control group.

Pathology:
Test item-related gross lesions were noted mainly in the kidneys, ureters and urinary bladders of animals of the HD group. Males were more affected than females. The findings consisted mainly of renal pelvis dilatation (in

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one decedent male it was described as enlarged kidney and abnormal consistency), ureter dilatation, and thickening of the urinary bladder wall.

Organ Weight:
Kidney weights were moderately increased in male and female animals of the HD group, when compared to controls. Thymus weight was slightly lower in male and female animals of the HD group, when compared to controls. Prostate gland was slightly lower in the HD group when compared to controls. A tendency towards increased liver weight (approx. 10 % above controls) was observed in female animals of the MD and HD groups.

Histopathology:
Histologically, test item-related lesions were noted in main test and recovery animals.

Under the conditions of this study, one male at 360 mg/kg bw/day was sacrificed during the course of the study. The cause of morbidity was deemed to be an induced backflow nephrosis.

Test item-related gross lesions consisted in kidneys of renal pelvis dilatation and of ureter dilatation, and thickening of the urinary bladder wall.

Histologically, test item-related lesions were noted in main test and recovery animals in:

Kidneys:
- increased incidence of pelvic dilation in males at 40 up to 360 mg/kg bw/day,
- tubular dilation in almost all males at 360 mg/kg bw/day,
- increased incidence of minimal tubular basophilia in males at 120 mg/kg bw/day, and in both sexes at 360 mg/kg bw/day,
- pyelitis in males at 120 mg/kg bw/day,
- pyelitis and interstitial inflammation, interstitial fibrosis and papillary necrosis in both sexes at 360 mg/kg bw/day,
- increased incidence of pelvic dilation in males at all doses,
- tubular dilation in almost all males at 360 mg/kg bw/day,
- urothelial hyperplasia in two males at 120 mg/kg bw/day, and in all males and four females at 360 mg/kg bw/day.

Ureter:
- dilation of ureters in one male at 120 mg/kg bw/day, and in all males and three females at 360 mg/kg bw/day,
- mucosal and/or muscularis hyperplasia, and/or inflammation in several animals at 360 mg/kg bw/day.

Urinary bladder:
- diffuse urothelial hyperplasia in both sexes at 120 and 360 mg/kg bw/day,
- increased incidence and severity of mononuclear cell foci.

Urethra:
- In one male at 360 mg/kg bw/day, the urethra was affected by moderate urothelial hyperplasia accompanied by a minimal subacute inflammation. At some locations, in mucosal folds, a precipitation of an unknown material was seen.

Adrenal cortices:
- diffuse cortical hypertrophy in females at 40 mg/kg bw/day, and in both sexes at 120 and 360 mg/kg bw/day (main test only).

Thymus:
- increased thymic atrophy in females at 40 mg/kg bw/day, and in both sexes at 120 and 360 mg/kg bw/day (main test only).

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There were no abnormalities in the male reproductive organs. There were no findings, during sperm staging of PAS stained testicular sections. There were no abnormalities in the female reproductive organs.

Dose Formulation Analysis
Nominal concentrations were confirmed for all dose groups, as measured concentrations were within acceptance criterion of 15%.

Conclusion
On the basis of this combined repeated dose oral toxicity and reproduction/ developmental toxicity screening test (OECD TG 422) with Triethoxyphenylsilane in male and female Wistar rats with dose levels of 40, 120, and 360 mg/kg bw/day the following conclusions can be made:

One HD rat (360 mg/kg bw/day) was sacrificed in moribund condition on day 15. As to histopathological evaluation, it is assumed to be a consequence of backflow nephrosis and considered to be treatment related.

There were no treatment related clinical signs throughout the treatment period up to 360 mg/kg bw/day. There were no treatment related functional observations changes at the end of treatment and recovery period. Treatment related adverse effects of the test item were found on male and female body weight and food consumption mainly at 360 mg/kg bw/day. Haematology and coagulation, clinical biochemistry, and urinalysis parameters were not affected by the treatment in both genders.

At scheduled necropsy treatment related gross macroscopic findings were noted in kidneys, urinary bladder, adrenals and thymus. Changes in respective organ weights are considered to be treatment related at 120 and 360 mg/kg bw/day.

Test item-related gross lesions of the kidneys consisted of renal pelvis dilatation (in one decedent recovery male it was described as enlarged kidney and abnormal consistency). Histologically, the incidence of pelvic dilation increased in males at 40 up to 360 mg/kg bw/day, and tubular dilation was noted in almost all males at 360 mg/kg bw/day. Degenerative and inflammatory lesions observed at 120 and 360 mg/kg/ bw/day, consisted of increased incidences and/or severities of tubular basophilia, pyelitis, and, at 360 mg/kg bw/day, of interstitial inflammation, interstitial fibrosis and papillary necrosis. Furthermore, there was urothelial hyperplasia in two males at 120 mg/kg bw/day, and in all males and four females at 360 mg/kg bw/day. Males were more affected than females. The findings were still present after the recovery period.

There were also ureter dilatation and thickening of the urinary bladder wall noted at necropsy. Histologically, ureter dilation was observed for one male at 120 mg/kg bw/day, and from all males and three females at 360 mg/kg bw/day, associated in some cases with mucosal and/or muscularis hyperplasia, and/or inflammation at 360 mg/kg bw/day. The highest degree of mucosal hyperplasia was noted at the most distal portions of the ureters. In the urinary bladder, there was diffuse urothelial hyperplasia in both sexes at 120 and 360 mg/kg bw/day. This finding was associated with an increased incidence and severity of mononuclear cell foci.

In one male, the urethra was found within the prostate tissue. The urothelium showed a moderate hyperplasia accompanied by a minimal subacute inflammation. At some locations, a precipitation of an unknown material was seen in the mucosal folds.

This precipitation in the urethra may be the test item, or a metabolite of the test item. The precipitation was noted by chance only due to the unusual circumstances to observe the urethra within the prostate gland. This finding may explain the higher grading of urothelial hyperplasia at more distal parts of the urinary system. Precipitation is likely to have caused irritation of the urothelium that results in backflow nephrosis with dilatation of the renal pelvis (hydronephrosis) and tubular dilation (nephrohydrosis).

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Stress-related lesions were noted in the adrenals by cortical hypertrophy and thymus by increased thymic atrophy.

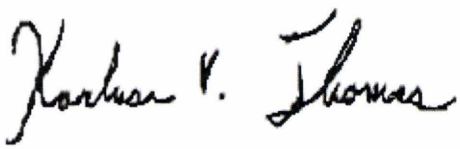
There were no effects on estrous cyclicity, litter data, litter weight data, precoital interval and duration of gestation, pre and post-natal data, reproductive indices, pup survival data, pup anogenital distance and nipple retention, or pup thyroid weight. Thyroid hormone analysis in parental males and pups sacrificed on PND 13 and males sacrificed at the end of recovery period were not different from control animals. Pup external findings were not different from controls for all treated groups.

No specific histopathological lesions were noted in the reproductive system organs from treated males and females.

At this time, neither SEHSC nor any of its member companies has made a determination as to whether a significant risk or injury to human health or the environment is actually presented by the findings. This information is being submitted in accordance with the Agency's TSCA 8(e) requirements and should therefore discharge any 8(e) responsibilities that might exist.

If you have any questions regarding this submission, please contact me at (202) 249-6197 or karluss_thomas@americanchemistry.com.

Sincerely,



Karluss Thomas
Sr. Director

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